
Article:
Howsley, P. and Levita, L. (2018) Developmental changes in the cortical sources of spontaneous alpha throughout adolescence. International Journal of Psychophysiology , 133. pp. 91-101. ISSN 0167-8760

https://doi.org/10.1016/j.ijpsycho.2018.08.003

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PII: S0167-8760(18)30042-4
DOI: doi:10.1016/j.ijpsycho.2018.08.003
Reference: INTPSY 11477

To appear in: *International Journal of Psychophysiology*

Received date: 1 February 2018
Revised date: 6 August 2018
Accepted date: 7 August 2018

Please cite this article as: Philippa Howsley, Liat Levita , Developmental changes in the cortical sources of spontaneous alpha throughout adolescence. Intpsy (2018), doi:10.1016/j.ijpsycho.2018.08.003

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Developmental changes in the cortical sources of spontaneous alpha throughout adolescence

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Abstract

This study investigated age-, gender-, and puberty-related changes in two cortical sources of spontaneous alpha during eyes-open and eyes-closed conditions in a cohort of adolescents aged 9-23 years. In total, 29 preadolescents (9-12 years, 14 females), 29 mid-adolescents (13-17 years, 14 females), and 33 late adolescents (18-23 years, 17 females) had their resting brain activity measured using electroencephalography (EEG) during eyes-open and eyes-closed conditions. Standardised Low Resolution Brain Electromagnetic Tomography (sLORETA) was used to estimate the cortical sources of spontaneous alpha. Two cortical sources were chosen as regions of interest (ROIs): prefrontal cortex and occipital cortex. Significant age-related changes in the cortical sources of alpha were found, particularly in prefrontal regions; prefrontal alpha power was greater during the eyes-open condition compared to the eyes-closed condition for late adolescents, but equivalent across the eyes-open and eyes-closed conditions for both pre- and mid-adolescents. In addition, more advanced pubertal stage predicted reduced alpha power in male, but not female, adolescents aged 9-17 years. This study provides an important initial step towards understanding developmental changes in the cortical sources of spontaneous alpha in the typically developing brain. Moreover, the results from this study underscore the need to tease out the effects of age, gender, and puberty when examining the cortical sources of alpha during the adolescent period.

Keywords: adolescence, alpha, EEG, puberty, resting state, sLORETA

1. Introduction

1.1. Adolescent brain development

The human brain undergoes substantial structural changes during adolescence. Structural magnetic resonance imaging (sMRI) studies have consistently documented a decrease in grey matter volume (Giedd, 2004; Gogtay *et al*., 2004; Mills *et al*., 2016) and an increase in white matter volume (Barnea-Goraly *et al*., 2005; Giedd, 2004) throughout the adolescent period. These changes in grey and white matter are thought to reflect the removal of superfluous synapses and their associated neuropil, myelination, and/or increases in axon size (Paus *et al*., 2001; Sowell, Thompson, Holmes, Jernigan & Toga, 1999; Sowell, Trauner, Gamst & Jernigan, 2002). These structural changes largely occur in a back-to-front order, with posterior cortical regions maturing earlier in development than anterior cortical regions (Gogtay *et al*., 2004). There is also evidence that grey matter volume in subcortical structures matures earlier in development than in cortical prefrontal regions (Mills, Goddings, Clasen, Giedd & Blakemore, 2014). Thus, compared to other cortical and subcortical regions, the prefrontal cortex (PFC) undergoes a protracted development across adolescence, which extends into the third decade of life (Giedd, 2004; Gotgay *et al*., 2004; Huttenlocher, 1979; Mills *et al*., 2016).

Corresponding age-related changes in scalp-recorded electroencephalography (EEG) activity have been widely reported (see Segalowitz, Santesso & Jetha, 2010 for a review). Overall, studies show that the absolute EEG power decreases with age during childhood and adolescence (Bresnahan, Anderson & Barry, 1999; Dustman, Shearer & Emmerson, 1999), and that these decreases coincide with developmental reductions in grey matter volume (Whitford *et al*., 2007). Moreover, changes in the distribution of EEG activity, where slower activity is replaced with faster activity, begin in occipital cortical regions and progress to frontal cortical regions (Dustman *et al*., 1999; Gasser, Jennen-Steinmetz, Sroka, Verleger & Möcks, 1988a; Gasser, Verleger, Bächer & Sroka, 1988b; Matoušek & Petersén, 1973). Consistently, there is also evidence that prefrontal EEG activity continues to mature during late adolescence (Hudspeth & Pribram, 1990). Finally, augmentation of white matter volume during adolescence is thought to result in age-related increases in peak EEG frequency and EEG coherence, and consequently more efficient and faster neuronal communication

(Segalowitz *et al*., 2010).

1.2. Spontaneous alpha

Spontaneous EEG activity is recorded while participants are awake and resting with their eyes open or closed and measures the endogenous fluctuations of cortical activity. The most dominant spontaneous EEG frequency is alpha (Klimesch, 1999). The alpha rhythm oscillates in the frequency range between 8 and 13 Hz, and has maximal amplitude over occipital regions when individuals are awake and resting with their eyes closed (Berger, 1929). Alpha power is inversely related to cortical activity (Haegens, Nácher, Luna, Romo & Jensen, 2011; Shagass, 1972), and studies suggest that individual differences in alpha power are largely determined by genetic factors (Smit, Wright, Hansell, Geffen & Martin, 2006; Van Beijsterveldt & Van Baal, 2002). Developmentally, the peak frequency of spontaneous alpha increases from approximately 3 Hz in early infancy to the adult peak frequency of 10 Hz by early adolescence (Lindsley, 1939; Marshall, Bar-Haim & Fox, 2002; Niedermeyer, 1997; Somsen, van't Klooster, van der Molen, van Leeuwen & Licht, 1997; Stroganova, Orekhova & Posikera, 1999). Moreover, spontaneous alpha power decreases across all areas of the scalp during childhood and adolescence (Bresnahan *et al*., 1999; Dustman *et al*., 1999). Alpha power is therefore less stable during adolescence than adulthood (Tenke *et al*., 2018).

EEG studies examining the functional significance of alpha have consistently reported that alpha power is associated with performance on tasks measuring cognitive function (Boiten, Sergeant & Geuze, 1992), memory encoding and retrieval (Klimesch, Doppelmayr, Schimke & Ripper, 1997; Vogt, Klimesch & Doppelmayr, 1998), and attention (Cooper, Croft, Dominey, Burgess & Gruzelier, 2003; Van Winsun, Sergeant & Geuze, 1984). Moreover, these studies report that alpha synchronises (increases) in task irrelevant cortical areas and desynchronises (decreases) in task relevant cortical areas, and that greater alpha desynchronisation is associated with better task performance (e.g., Klimesch *et al*., 1997). There is also evidence that alpha power is associated with general intelligence (Alexander, Boyle & Benbow, 1996; Jaušovec & Jaušovec, 2000) and theory of mind in children (Sabbagh, Bowman, Evraire & Ito, 2009). Repetitive transcranial magnetic stimulation (rTMS) studies also support the idea that alpha is integral to cognitive functioning. For instance, Klimesch,

Sauseng & Gerloff (2003) found that rTMS over the frontal and parietal cortices at 1 Hz above participants' individual peak alpha frequency significantly improved cognitive task performance. Taken together, these findings clearly demonstrate that alpha power has an active role in gating relevant and irrelevant brain activity to facilitate efficient neuronal processing and cognitive functioning (Foxe & Snyder, 2011; Jensen, Bonnefond & VanRullen, 2012; Klimesch, 1999; Klimesch, Sauseng & Hanslmayr, 2007).

1.3. Sources of spontaneous alpha

Scalp-recorded EEG activity represents activity from a number of spatially dispersed cortical and subcortical sources. Thus, the underlying cortical and subcortical sources of spontaneous alpha cannot be determined from scalp-recorded EEG activity. More recent work has therefore aimed to identify the cortical and subcortical sources of spontaneous alpha. To date, the vast majority of studies have investigated the sources of spontaneous alpha in healthy adults with their eyes closed (Cuspineda *et al*., 2009; de Munck *et al*., 2007; Feige *et al*., 2005; Goldman, Stern, Engel Jr & Cohen, 2002; Lüchinger, Michels, Martin & Brandeis, 2011). Together, these studies provide convincing evidence to suggest that the thalamus and occipital-parietal cortices are the primary sources of spontaneous alpha during eyes-closed conditions. However, several studies have reported that frontal and temporal cortical regions also have a role in generating spontaneous alpha during eyes-closed conditions (Cuspineda *et al*., 2009; Goldman *et al*., 2002; Wu, Eichele & Calhoun, 2010). While less work has examined the sources of spontaneous alpha in healthy adults during eyes-open conditions, the initial work suggests that a wider neural network is engaged when the eyes are open compared to when the eyes are closed (Lüchinger *et al*., 2011). There is also evidence that the shift from eyes-closed to eyes-open significantly reduces the haemodynamic response in the thalamus and across frontal, temporal, parietal and occipital cortical regions (Feige *et al*., 2005; Wu *et al*., 2010).

These findings collectively suggest that cortical regions and the thalamus have a role in generating spontaneous alpha during eyes open and eyes closed conditions. It has been reported that the alpha rhythm can be detected slightly earlier in the thalamus than in the cortex (de Munck *et al*., 2007), suggesting that the thalamus generates the alpha rhythm and subsequently induces

synchronised alpha activity in the cortex. However, there is also work to suggest that cortico-cortical networks that are independent of thalamic input generate spontaneous alpha (Lopes da Silva, Vos, Mooibroek & Van Rotterdam, 1980). The evidence to date therefore suggests that spontaneous alpha is generated by a combination of thalamo-cortical and cortico-cortical networks (Başar, Schürmann, Başar-Eroglu & Karakas, 1997; Lopes da Silva & Van Leeuwen, 1977; Steriade, Gloor, Llinas, Lopes da Silva & Mesulam, 1990).

1.4. Age- and gender-related changes in the sources of spontaneous alpha

To the authors' knowledge, only one study has examined age-related changes in the sources of spontaneous alpha during adolescence (Lüchinger *et al*., 2011). Lüchinger *et al*. (2011) recorded simultaneous EEG-fMRI in healthy adolescents (15 years) and young adults (25 years) and found that adolescents and young adults had comparable patterns of cortical and subcortical alpha activity during both eyes-open and eyes-closed conditions. While Lüchinger *et al*.'s (2011) study represents a first step in understanding the sources of spontaneous alpha during adolescence, the sample only included 15 and 25 year olds and thus the findings cannot be generalised to adolescents of other ages. Moreover, Lüchinger *et al*. (2011) did not explore potential gender differences in the sources of spontaneous alpha. There are significant gender differences in cortical and thalamic grey matter volume during adolescence (see Lenroot & Giedd, 2010 for a review) and grey matter volume tends to peak 1-2 years earlier in development in females than males (Lenroot *et al*., 2007). Consistently, gender differences have been reported in scalp-recorded EEG resting alpha in children, adolescents, and adults (Barry *et al*., 2004; Barry & Clarke, 2009; Jaušovec & Jaušovec, 2010). Consequently, additional work is needed to explore potential gender differences in the sources of spontaneous alpha throughout the course of adolescence.

1.5. Puberty-related changes in sources of spontaneous alpha

Puberty is a developmental period encompassing the physical changes that are necessary for sexual maturation (Spear, 2000). The onset of puberty varies markedly between individuals; puberty can begin any time between 8-13 years for healthy females and 9-14 years for healthy males

(Sørensen *et al*., 2013). There are an increasing number of studies reporting that pubertal influences contribute to gender differences in cortical grey matter during adolescence (Bramen *et al*., 2011; Neufang *et al*., 2009; Peper *et al*., 2009). Gender differences in thalamic grey matter during adolescence have also been found (Sowell *et al*., 2002) but, in contrast to cortical grey matter, such differences do not seem to be associated with puberty (Bramen *et al*., 2011; Peper *et al*., 2009). Given that alpha is generated by widespread cortical regions in addition to the thalamus (Cuspineda *et al*., 2009), is possible that the effects of puberty on cortical grey matter development may in turn influence the development of spontaneous alpha. Despite this, no study has yet explored the relationship between puberty and the cortical sources of spontaneous alpha during adolescence.

1.6. The present study

This study aimed to investigate the age-, gender-, and puberty-related changes in the cortical sources of spontaneous alpha in a cohort of adolescents aged 9-23 years. Two cortical sources were chosen as regions of interest (ROIs): the PFC and occipital cortex. The PFC is a cortical source of spontaneous alpha during both eyes-open and eyes-closed conditions (Cuspineda *et al*., 2009; Lüchinger *et al*., 2011), and continues to develop structurally (Gotgay *et al*., 2004; Mills *et al*., 2014) and functionally (Casey, Jones & Somerville, 2011) throughout adolescence. For example, functional MRI studies report that prefrontal cortical activity becomes less diffuse and more focal during childhood and adolescence (Casey *et al*., 1997; Durston *et al*., 2006). Given that alpha has a clear role in inhibiting irrelevant brain activity (Jensen *et al*., 2012; Klimesch *et al*., 2007), it is possible that alpha is one mechanism underlying such developmental changes in prefrontal activity. The PFC is therefore a good candidate for examining age-related changes in the cortical sources of spontaneous alpha during adolescence. The occipital cortex was selected as a ROI since it structurally matures relatively early on in development (Giedd, 2004; Gogtay *et al*., 2004) and is thought to be one of the primary cortical generators of alpha in adolescents and adults (Cuspineda *et al*., 2009; Lüchinger *et al*., 2011).

In light of previous literature, four hypotheses were made. Firstly, due to reductions in cortical grey matter across adolescence (Gogtay *et al*., 2004; Mills *et al*., 2016), it was hypothesised

that absolute alpha power would decrease during the course of adolescence irrespective of condition and region (Bresnahan *et al*., 1999; Dustman *et al*., 1999; Whitford *et al*., 2007). Secondly, due to the prolonged structural and functional development of the PFC (Durston *et al*., 2006; Gotgay *et al*., 2004; Hudspeth & Pribram, 1990), it was hypothesised that occipital alpha power would mature earlier on in adolescence than PFC alpha power. Thirdly, since grey matter volumes peak earlier in females than males (Giedd, 2004; Gogtay *et al*., 2004), it was hypothesised that the maturation of prefrontal and occipital alpha power would be faster in females than in males. Finally, since cortical grey matter volume decreases throughout adolescence (Gogtay *et al*., 2004; Mills *et al*., 2016), it was hypothesised that more advanced pubertal stage would be associated with less alpha power in prefrontal and occipital regions for both males and females.

2. Materials and Methods

2.1. Participants

Ninety-four volunteers aged 9-23 years participated in this study. Three participants were excluded due to insufficient data following artefact rejection (3 females aged 9, 17, and 21 years). Participant demographics for the final sample are reported in Table 1. Participants were split into three age groups in order to assess how the prefrontal and occipital cortical sources of alpha change between three distinct stages of adolescence: preadolescence (9-12 years); mid-adolescence (13-17 years); and late adolescence (18-23 years). All participants were right-handed, native English speakers, had normal or corrected-to-normal vision, normal hearing, and no current or previous neurological, psychiatric, or medical conditions. Participants were recruited through the University of Sheffield and local advertising. Written informed consent was received from all participants, as well as from a parent or guardian of participants aged 9-17 years. Participants received £5 for taking part and were debriefed upon completion of the study. The study was approved by the Department of Psychology University of Sheffield Ethics Committee.

The Pubertal Development Scale (PDS; Petersen, Crockett, Richards & Boxer, 1988) was used to measure current pubertal stage. Puberty is largely complete by 17 years of age (Dorn, Dahl, Woodward & Biro, 2006) and therefore only participants aged 9-17 years completed the PDS. Males

rated their growth in height, skin changes, body and facial hair growth, and voice changes while females rated their growth in height, skin changes, body hair growth, breast development, and menarche status. Each item (except menarche status) was rated on a four-point scale: 1 = not yet started; 2 = barely started; 3 = changes are underway; 4 = seems complete. Points for each item were averaged to give a PDS score. A higher PDS score indicated a more advanced pubertal stage. An independent t-test revealed that PDS scores were comparable for males (M = 2.30, 95% CI [2.02, 2.55]) and females (M = 2.73, 95% CI [2.45, 3.00]) ($t(56) = 2.05$, $p = 0.050$), indicating that the males and females in this sample were at a similar stage in their pubertal development.

Table 1 about here

2.2. EEG recording

In order to maximise the quality of EEG recordings, participants were asked to attend EEG sessions with clean hair free from conditioner and hair products, to wear comfortable and loose fitting clothing, to wear contact lenses instead of glasses if appropriate, and to reschedule if unwell or tired. Participants were not asked to limit their caffeine, alcohol or tobacco use or to report their recent sleep activity.

The EEG signals were recorded using Biosemi Active Two 64 channel electrode caps and Biosemi Pin-Type Ag-AgCl active electrodes (BioSemi, Amsterdam, Netherlands) that were fitted according to the 10-20 electrode system. Biosemi caps also include two additional electrodes, Common Mode Sense (CMS) and Driven Right Leg (DRL), that are positioned either side of the POz electrode. The DRL electrode replaces the conventional ground electrode and the CMS electrode acts as an online reference. Electrooculography (EOG) signals were recorded using four Biosemi flat active electrodes placed on participants' temples and above and below their left eye. EEG and EOG signals were amplified using the Biosemi ActiveTwo AD-Box. Electrode offsets were stable and kept between ±25 μV. EEG and EOG signals were recorded continuously with a sampling rate of 2048 Hz

and without a reference electrode or online filters. To reduce the effects of environmental electrical noise, participants sat in a quiet, dimly lit electrically shielded room. The room was kept cool using air conditioning to minimise slow drifts in the recording resulting from sweat (Light *et al*., 2010).

Participants were instructed to relax and stay as still as possible. Six one-minute intervals of resting state EEG data were recorded. Three minutes of data were recorded while participants had their eyes open and three minutes of data were recorded while participants had their eyes open in an alternating order (open-closed-open-closed-open-closed). MATLAB 2012a was used to time the one-minute intervals of data and send triggers to the EEG recording. The experimenter closely monitored the laboratory computers during the recording session and verbally instructed participants when to open or close their eyes. To allow the experimenter to instruct the participants when to open and close their eyes an additional 10 seconds of data was recorded between each interval, which was subsequently deleted from the analysis.

2.3. EEG processing

All EEG processing was conducted offline. EEG data were downsampled from 2048 to 512 Hz using Biosemi's decimator tool. Biosemi's decimator tool applies a fifth order sinc filter to prevent aliasing. The eyes-open and eyes-closed conditions were analysed separately but followed an identical preprocessing stream. EEG data were imported into EEGLAB v13.5.4b (Delorme & Makeig, 2004) using Cz (the vertex) as the reference to maximise the signal-to-noise ratio. ERPLAB v5.0 (Lopez-Calderon & Luck, 2014) was used to remove the direct current offset and band-pass filter the continuous EEG data between 0.1 and 30 Hz. EEGLAB was used for the subsequent analyses. Electrode channels that resulted in the rejection of more than 25 per cent of data were deleted and subsequently interpolated using the surrounding channels to ensure that all participants had 64 channels available for analysis. Continuous EEG data were epoched into two-second epochs that overlapped by 25 per cent to prevent data loss. Finally, any remaining artefacts, such as eye and muscle movements, were removed by rejecting epochs with amplitude differences exceeding ± 150 μV.

2.4. Spectral analysis

In line with previous developmental studies (e.g., Barry, Clarke, Johnstone & Brown, 2009), the alpha frequency band was defined as 8-13 Hz for all groups. A fast Fourier Transform, using a Hamming window with tapered edges, was applied to each artefact-free epoch to compute estimates of spectral power (μV^2). Spectral power values were subsequently converted to power density (μV^2/Hz) in the alpha frequency band. Peak frequency in the alpha frequency band across all electrode sites was calculated for all groups for both conditions (Table 1). No significant differences in peak alpha frequency were found between age groups ($F(2, 85) = 1.52$, $p = 0.225$, $\eta_p^2 = 0.04$) or genders ($F(1, 85) = 0.02$, $p = 0.876$, $\eta_p^2 = 0.00$), suggesting that peak alpha frequency was comparable across groups.

2.5. Source localisation

Standardised Low Resolution Brain Electromagnetic Tomography (sLORETA; Pascual-Marqui, 2002) is a widely used and validated source localisation solution (Mobascher *et al*., 2009; Olbrich *et al*., 2009). sLORETA provides a three-dimensional distributed, linear, minimum norm inverse solution that computes current source density (CSD) estimates from scalp-recorded EEG activity. sLORETA partitions the cortical grey matter into 6239 voxels (5 mm resolution) based on a realistic head model (Fuchs, Kastner, Wagner, Hawes & Ebersole, 2002) using the Montreal Neurological Institute 152 (MNI152) template (Mazziotta *et al*., 2001) as determined by the probabilistic Talairach atlas (Lancaster *et al*., 2000).

Notably, the sLORETA solution space is largely limited to cortical grey matter and is unable to examine subcortical structures such as the thalamus. It should also be noted that the MNI152 template is an average of sMRI scans from healthy adults and consequently may not be an ideal fit for children and adolescents. However, there are currently no source localisation solutions that offer developmentally appropriate sMRI templates and sLORETA has been successfully used in previous developmental studies with similar age ranges (e.g., Chan, Han, Sze & Lau, 2015). In light of these considerations, sLORETA was deemed an appropriate source localisation solution for this study.

sLORETA version 20081104 was downloaded from http://www.uzh.ch/keyinst/loreta.htm.

The artefact-free epochs were given as an input to sLORETA to compute EEG cross-spectra for each participant. The cross-spectra were then used to estimate the corresponding three-dimensional CSD ($\mu A/mm^2$) for the alpha frequency band (8-13 Hz). The sLORETA maps for absolute alpha power for the eyes-open and eyes-closed conditions are displayed in Figure 1. In the present study, alpha activity was predominately localised to parietal-occipital regions during the eyes-closed condition for all groups. This is highly consistent with previous work (Cuspineda *et al*., 2009; Lüchinger *et al*., 2011) and therefore suggests that sLORETA provided an accurate source localisation solution in this cohort of adolescents. Brodmann areas (BA) were used to define two ROIs: the PFC (BA8, BA9, BA10, BA11, BA44, BA45, BA46, BA47) and occipital cortex (BA17, BA18, BA19). All voxels within BA were used in the ROIs. The two ROIs were used in all subsequent statistical analyses.

Figure 1 about here

The cross-spectra were also used to calculate absolute power ($\mu A/mm^2$) for the delta (1-3.5 Hz), theta (4-7.5 Hz), and beta (13.5-30 Hz) frequency bands for the prefrontal and occipital ROIs during eyes-closed and eyes-open conditions (Supplementary Figure 1). The relative power (%) of each frequency band was subsequently calculated to determine the relative contribution of alpha to the total power in each ROI (Figure 2). Relative power was calculated by dividing absolute power for each frequency band by total power (sum of absolute delta, theta, alpha, and beta) and multiplying by 100.

Figure 2 about here

2.6. Statistical analyses

Statistical analyses were conducted using IBM SPSS v22.0. A 2 x 2 mixed-design analysis of variance (ANOVA) was used to examine age- and gender-related changes in the two cortical sources of spontaneous alpha during the eyes-open and eyes-closed conditions. *Location* (PFC *vs.* occipital cortex) and *Condition* (eyes-open *vs.* eyes-closed) were the within-group factors, and *Age Group* (preadolescents *vs.* mid-adolescents *vs.* late adolescents) and *Gender* (females *vs.* males) were the between-group factors. Significant interactions were followed up with paired t-tests (Table 2). T-tests were bootstrapped using bias-corrected and accelerated 95% confidence intervals based on 1000 samples. The Benjamini-Hochberg procedure (Benjamini & Hochberg, 1995) was used to correct ANOVA pairwise comparisons and t-tests with a false discovery rate (FDR) of 0.1. The group means and bootstrapped 95% confidence intervals for absolute alpha power in the prefrontal and occipital ROIs during the eyes-open and eyes-closed conditions are displayed in Figure 3.

Next, hierarchical polynomial regression analyses were conducted to examine puberty-related changes in the two cortical sources of spontaneous alpha during the eyes-open and eyes-closed conditions. Given that the age of pubertal onset is highly variable between individuals (Sørensen *et al*., 2013), it is possible that categorising adolescents into age groups may confound potential relationships between puberty and alpha. Thus, the relationships between puberty and alpha were examined in 9-17 year old females (M = 12.71 years, SD = 2.26; n = 28) and males (M = 12.67 years, SD = 2.55; n = 30) using age as a continuous variable. Regression analyses were conducted with the following dependent variables: eyes-open prefrontal alpha power; eyes-closed prefrontal alpha power; eyes-open occipital alpha power; and eyes-closed occipital alpha power. To tease out the confounding effects of chronological age on pubertal development, age was entered into the first block of the regression model as a control variable and PDS scores were entered into the second block. Regression analyses were bootstrapped using bias-corrected and accelerated 95% confidence intervals based on 1000 samples. To correct for multiple comparisons, the Benjamini-Hochberg procedure (Benjamini & Hochberg, 1995) was applied to regression analyses with an FDR of 0.1.

3. Results

3.1. Age- and gender-related changes in the sources of spontaneous alpha

A main effect of *Age Group* ($F(2, 85) = 8.35$, $p < 0.001$, $\eta_p^2 = 0.16$) showed that preadolescents (M = 0.43, 95% CI [0.32, 0.53]) had more overall alpha power than both mid-adolescents (M = 0.25, 95% CI [0.14, 0.35]) ($p = 0.018$) and late adolescents (M = 0.13, 95% CI [0.03, 0.23]) ($p < 0.001$). In contrast, no difference in overall alpha power was found between mid-adolescents and late adolescents ($p = 0.120$). The main effect of *Location* ($F(1, 85) = 46.24$, $p < 0.001$, $\eta_p^2 = 0.35$) revealed that there was more alpha power in the occipital cortex (M = 0.45, 95% CI [0.34, 0.56]) than in the PFC (M = 0.09, 95% CI [0.08, 0.10]). Finally, the main effect of *Condition* ($F(1, 85) = 33.16$, $p < 0.001$, $\eta_p^2 = 0.28$) showed that there was more alpha power during the eyes-closed condition (M = 0.41, 95% CI [0.31, 0.52]) than the eyes-open condition (M = 0.13, 95% CI [0.11, 0.15]).

Figure 3 about here

Four interactions were also found. Firstly, the *Location* by *Age Group* interaction ($F(2, 85) = 6.78$, $p = 0.002$, $\eta_p^2 = 0.14$) revealed that all age groups had more alpha power in the occipital cortex than in the PFC. Secondly, the *Condition* by *Age Group* interaction ($F(2, 85) = 5.83$, $p = 0.004$, $\eta_p^2 = 0.12$) showed that all age groups had more alpha power during the eyes-closed condition than in the eyes-open condition. Thirdly, the *Location* by *Condition* interaction ($F(1, 85) = 43.71$, $p < 0.001$, $\eta_p^2 = 0.34$) showed that alpha power was comparable between the eyes-open and eyes-closed conditions in the PFC but significantly greater during the eyes-closed condition than the eyes-open condition in the occipital cortex. Finally, there was a *Location* by *Condition* by *Age Group* interaction ($F(2, 85) = 5.88$, $p = 0.004$, $\eta_p^2 = 0.12$). Paired t-tests revealed that prefrontal alpha power was comparable during

the eyes-open and eyes-closed conditions for both preadolescents and mid-adolescents. By contrast, late adolescents had significantly more prefrontal alpha power during the eyes-open condition compared to the eyes-closed condition. In contrast to the PFC, all age groups had significantly more alpha power in the occipital cortex during the eyes-closed condition compared to the eyes-open condition. No other main effects or interactions reached significance.

Table 2 about here

3.2. Puberty-related changes in the sources of spontaneous alpha

Alpha power in the PFC and occipital cortex was not significantly predicted by pubertal stage for females. In contrast, alpha power in the PFC and occipital cortex was significantly predicted by pubertal stage for males. Specifically, prefrontal alpha power was significantly predicted by pubertal stage during the eyes-closed condition (ΔR^2 = 21.1%, β = -0.73, p = 0.009) but not during the eyes-open condition (ΔR^2 = 8.4%, β = -0.46, p = 0.080). In comparison, occipital alpha power was significantly predicted by pubertal stage during both the eyes-closed condition (ΔR^2 = 17.7%, β = -0.67, p = 0.021) and the eyes-open condition (ΔR^2 = 26.8%, β = -0.82, p = 0.004). Together, these findings reveal that prefrontal and occipital alpha power decreased with advancing pubertal stage in males, suggesting that puberty has a significant influence on the development of spontaneous alpha during adolescence that is independent of chronological age but dependent on gender. The partial regression plots for males are displayed in Figure 4.

Figure 4 about here

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4. Discussion

This study investigated age-, gender-, and puberty-related changes in two cortical sources of spontaneous alpha in a cohort of adolescents aged 9-23 years. Overall, the findings revealed significant age-related changes, particularly in prefrontal regions, and that more advanced pubertal stage was associated with a reduction in alpha power in both prefrontal and occipital regions for males but not females.

4.1. Age- and gender-related changes in the sources of spontaneous alpha

As predicted, alpha power decreased from preadolescence to mid-adolescence irrespective of region and condition. However, no significant decreases in alpha power were found from mid- to late adolescence. Such decreases in alpha power are likely to reflect the reduction in cortical grey matter during adolescence (Segalowitz *et al*., 2010; Whitford *et al*., 2007). Developmental reductions in grey matter are thought to be steepest from childhood to early adolescence and more gradual across middle and late adolescence (Mills *et al*., 2016). It is therefore possible that the present study did not detect a significant change in alpha power between mid- and late adolescents because developmental reductions in grey matter changes had slowed down.

Critically, significant age-related differences were found in prefrontal alpha power. Specifically, prefrontal alpha power was greater during the eyes-open condition compared to the eyes-closed condition for late adolescents, but equivalent across the eyes-open and eyes-closed conditions for both preadolescents and mid-adolescents. Given that alpha power is inversely related to cortical activity (Haegens *et al*., 2011), these findings suggest that late adolescents had more cortical inhibition in the PFC when their eyes were open than closed. EEG (Mazaheri, Nieuwenhuis, van Dijk & Jensen, 2009) and combined EEG-TMS (Thut & Miniussi, 2009) studies have found that alpha activity prior to an event or stimulus significant impacts subsequent processing. For instance, Mazaheri *et al*. (2009) found that alpha power just before trials on a go-nogo task predicted whether participants made an error. In light of such findings, it is possible that more prefrontal alpha power (i.e., more prefrontal cortical inhibition) in late adolescents when their eyes are open is a preparatory mechanism used to efficiently process incoming stimuli. Future work is needed to assess whether

resting prefrontal alpha power during eyes-open conditions is a mechanism underlying normative changes in prefrontal cortical activity and associated cognitive functioning during adolescence (Blakemore & Choudhury, 2006; Luna, Garver, Urban, Lazar, & Sweeney, 2004).

Several studies have reported that EEG maturation during childhood and adolescence is not linear but instead occurs in growth spurts that may be linked to cognitive development (Hudspeth & Pribram, 1990; Somsen *et al*., 1997; Thatcher, Walker & Giudice, 1987; Thatcher, 199l, 1992, 1994). Alpha activity may also develop at different rates in the left and right hemisphere during childhood and adolescence (Thatcher *et al*., 1987). Future work should therefore examine whether the sources of alpha follow similar developmental trajectories during childhood and adolescence. Furthermore, there is a body of work suggesting that extrinsic factors, such as early traumatic experiences (Ito, Teicher, Glod & Ackerman, 1998; Teicher *et al*., 1997), have significant effects on the development of alpha activity. Thus, while studies have shown that alpha activity is largely heritable (Smit *et al*., 2006), subsequent research should also consider the effects of systemic factors on the development of alpha during childhood and adolescence.

The findings from the present study are contrary to Lüchinger *et al*.'s (2011) study. It is possible that this discrepancy can be accounted for by several methodological differences between the studies. Firstly, Lüchinger *et al*.'s (2011) study explored age, but not gender, differences between adolescents (15 years) and late adolescents (25 years) whereas the present study explored age and gender differences between preadolescents (9-12 years), mid-adolescents (13-17 years), and late adolescents (18-23 years). Moreover, Lüchinger *et al*.'s (2011) study only included 36 participants whereas the present study had a sample size of 91 participants. Secondly, Lüchinger *et al*.'s (2011) used combined EEG-fMRI whereas the present study used EEG source localisation. Finally, while Lüchinger *et al*. (2011) examined lower (8-10 Hz) and upper (10-13 Hz) alpha separately, the present study examined alpha using a single frequency range of 8-13 Hz.

While the present study found significant age differences in the cortical sources of alpha, no significant gender differences were found. However, Figures 1 and 3 suggest that there were considerable differences in the cortical sources of alpha between the males and females in this study. In particular, for occipital alpha power during the eyes-closed condition, mid-adolescent males more

strongly resembled preadolescents whereas mid-adolescent females more strongly resembled late adolescents (Figure 1). Moreover, the age-related changes in prefrontal alpha power during late adolescence appear to be driven by females (Figure 3). These findings are consistent with what is currently known about brain development during adolescence, whereby female brains mature slightly faster than male brains (Lenroot *et al*., 2007; Lenroot & Giedd, 2010). Finally, Figure 3 also suggested a u-shaped developmental trajectory for prefrontal alpha power during the eyes-open condition for females but not males; prefrontal alpha power appeared to reduce from preadolescence to mid-adolescence and subsequently increase from mid-adolescence to late adolescence. It is possible that the lack of statistical significance for such gender-related differences reflects high levels of variability in this sample. High levels of variability in resting state studies is commonly reported and is thought to result from participants engaging in a range of internal processes, such as spontaneous thoughts, memory retrieval, future planning, or daydreaming (Fox, Spreng, Ellamil, Andrews-Hanna & Christoff, 2015).

Notably, delta was the dominant frequency in prefrontal regions during eyes-open and eyes-closed conditions and in occipital regions during the eyes-open condition for all groups (Figure 2). Although delta power is most often associated with slow-wave sleep (e.g., Dang-Vu *et al*., 2008), recent studies in rodents (Vyazovskiy *et al*. 2011) and humans (Sachdev *et al*., 2015) have reported high levels of delta activity during quiet wakefulness. In the present study, participants were seated in a quiet, dimly lit room and instructed to relax. Thus, the EEG findings reported here were recorded under conditions of quiet wakefulness, which may account for the high levels of delta activity.

4.2. Puberty-related changes in the sources of spontaneous alpha

Unexpectedly, relationships between spontaneous alpha and pubertal stage were only observed for males. More advanced pubertal stage predicted less prefrontal alpha power during the eyes-closed condition as well as less occipital alpha power during the eyes-open and eyes-closed conditions in males aged 9-17 years (Figure 4). Puberty accounted for between 17.7 and 26.8 per cent of the variance in alpha power after controlling for chronological age, suggesting that pubertal stage had a considerable influence on the development of prefrontal and occipital alpha in this sample of

adolescent males.

Given that the relationships between puberty and spontaneous alpha were found only in males, it is possible to speculate that these relationships resulted from puberty-related changes in testosterone levels. While the present study measured current pubertal stage rather than testosterone levels, previous studies have reliably documented that testosterone levels in males increase with advancing pubertal stage (Biro, Lucky, Huster & Morrison, 1995; Shirtcliff, Dahl & Pollak, 2009). Testosterone levels have been associated with the development of cortical, but not thalamic, grey matter in adolescent males (e.g., Neufang *et al*., 2009). Thus, it is possible that the relationships between puberty and alpha found in the present study resulted from the influence of testosterone on cortical grey matter.

4.3. Study limitations

There are a number of study limitations that need to be considered. Firstly, participants were recruited from the local community in addition to the University of Sheffield in an attempt to recruit a more representative sample. However, it is possible that the final sample of participants may be biased towards higher achieving individuals and the results should be interpreted with this limitation in mind.

Secondly, the present study only examined prefrontal and occipital sources of alpha. There is clear evidence to suggest that parietal and temporal regions are also cortical sources of alpha (Cuspineda *et al*., 2009; Goldman *et al*., 2002), and therefore future work should aim to explore how the parietal and temporal sources of alpha change throughout adolescence, and how this compares to the development of prefrontal and occipital sources.

Thirdly, given that participants in resting state studies are instructed to relax with their eyes open or closed, it is plausible that the participants in this study were engaging in a number of internal processes (Fox *et al*., 2015). Moreover, it is possible that the type of internal processes, such as daydreaming or future planning, varied between the age groups in this study. Hence, the high levels of variability in this study may reflect that preadolescents, mid-adolescents, and late adolescents were engaging in a variety of different internal processes. Future work should therefore aim to tease out the

cortical and subcortical sources of alpha that are associated with different internal processes during quiet wakefulness in separate developmental age groups. One approach would be to measure alpha while participants engage in a series of directed internal processes. Critically however, younger participants may not have the capabilities to engage in such internally directed thoughts, and there is no overt, reliable measure to determine which internal process participants engaged in. Event-related studies may therefore provide a more accurate way of assessing the cortical and subcortical sources of alpha involved in distinct internal processes. Notably, delta was the dominant frequency in prefrontal regions during eyes-open and eyes-closed conditions and in occipital regions during the eyes-open condition for all groups (Figure 2). Differing levels of relative alpha power may be associated with different underlying cortical and subcortical sources and future work should therefore endeavour to assess such relationships.

4.4. Conclusions

The majority of previous studies examining the sources of spontaneous alpha have focused on the adult brain. However, a comprehensive understanding of the alpha rhythm can be only achieved by investigating alpha in maturing, evolving, emotional, and pathological brains (Başar, 2012). The present study therefore provides an important step towards understanding the development of spontaneous alpha in the typically developing brain. Moreover, the findings from this study emphasise the need to tease out the effects of age, gender, and puberty when examining how cortical activity changes throughout the adolescent period. Nonetheless, a great deal more research needs to be conducted before we have a complete understanding of the development and function of alpha in the maturing brain, and the mechanisms through which alpha influences cognitive, memory, and attentional processes. Future work should therefore aim to examine the cortical and subcortical generators of alpha in adolescents using concurrent EEG-fMRI.

Acknowledgments

We are grateful to Anna Kolesnik for help with data collection and Gordon Farquhar for assistance with the figures. We would also like to thank the participants who took part in this study.

Conflicts of Interest

The authors declare no conflicts of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Table 1

Participant characteristics

Age group	Gender	*n*	Age (years)			Peak alpha frequency (Hz)			
						Eyes-open		Eyes-closed	
			Range	*M*	*SD*	*M*	95% CI	*M*	95% CI
Preadolescents	Females	14	9-12	10.93	1.21	9.00	8.36, 9.64	9.57	9.09, 10.06
	Males	15	9-12	10.53	1.30	8.40	7.78, 9.02	9.27	8.80, 9.74
	All	29	9-12	10.72	1.25	8.70	8.26, 9.15	9.42	9.08, 9.76
Mid-adolescents	Females	14	13-17	14.50	1.51	8.93	8.29, 9.57	9.57	9.09, 10.06
	Males	15	13-17	14.80	1.42	9.33	8.72, 9.95	9.87	9.40, 10.34
	All	29	13-17	14.66	1.45	9.13	8.69, 9.58	9.72	9.38, 10.06
Late adolescents	Females	17	18-23	20.35	1.41	8.94	8.36, 9.52	9.71	9.27, 10.15
	Males	16	18-23	21.00	1.55	9.19	8.59, 9.79	9.50	9.05, 9.95
	All	33	18-23	20.67	1.49	9.06	8.65, 9.48	9.60	9.29, 9.92

Note. 95% CI = bootstrapped 95% confidence intervals. Peak alpha frequency was calculated across all electrode sites. No significant differences in peak alpha frequency were found between age groups ($p = 0.225$) or genders ($p = 0.876$).

Table 2

Follow up analyses for significant ANOVA interactions

			Paired t-test		
	M	95% CI	*df*	*t*	*p*
Age Group x *Location*					
Preadolescents PFC	0.13	0.10, 0.15	28	4.22	< 0.001
Preadolescents occipital cortex	0.73	0.47, 1.04			
Mid-adolescents PFC	0.07	0.06, 0.09	28	4.50	< 0.001
Mid-adolescents occipital cortex	0.43	0.28, 0.62			
Late adolescents PFC	0.07	0.05, 0.09	32	4.65	< 0.001
Late adolescents occipital cortex	0.20	0.16, 0.24			
Age Group x *Condition*					
Preadolescents eyes-open	0.18	0.14, 0.23	28	3.70	0.001
Preadolescents eyes-closed	0.67	0.40, 1.00			
Mid-adolescents eyes-open	0.11	0.08, 0.15	28	4.00	< 0.001
Mid-adolescents eyes-closed	0.39	0.25, 0.57			
Late adolescents eyes-open	0.09	0.07, 0.12	32	2.82	0.008
Late adolescents eyes-closed	0.17	0.13, 0.23			
Location x *Condition*					
PFC eyes-open	0.09	0.08, 0.11	90	1.59	0.116
PFC eyes-closed	0.08	0.07, 0.10			
Occipital cortex eyes-open	0.16	0.13, 0.19	90	5.76	< 0.001
Occipital cortex eyes-closed	0.73	0.53, 0.95			
Age Group x *Location* x *Condition*					
Preadolescents prefrontal eyes-open	0.13	0.10, 0.15	28	0.26	0.799
Preadolescents prefrontal eyes-closed	0.12	0.09, 0.15			
Preadolescents occipital eyes-open	0.24	0.18, 0.32	28	3.87	0.001
Preadolescents occipital eyes-closed	1.22	0.73, 1.84			
Mid-adolescents prefrontal eyes-open	0.07	0.05, 0.08	28	0.67	0.510
Mid-adolescents prefrontal eyes-closed	0.07	0.06, 0.08			
Mid-adolescents occipital eyes-open	0.15	0.10, 0.22	28	4.15	< 0.001
Mid-adolescents occipital eyes-closed	0.71	0.46, 1.00			
Late adolescents prefrontal eyes-open	0.09	0.06, 0.12	32	2.18	0.037
Late adolescents prefrontal eyes-closed	0.05	0.04, 0.06			
Late adolescents occipital eyes-open	0.10	0.08, 0.12	32	4.29	< 0.001
Late adolescents occipital eyes-closed	0.30	0.21, 0.40			

Note. PFC = prefrontal cortex; 95% CI = bootstrapped 95% confidence intervals. PFC and occipital absolute alpha power is measured in $\mu A/mm^2$.

Figure Captions

Figure 1. sLORETA maps for the alpha frequency band (8-13 Hz) during the eyes-open (**a**) and eyes-closed (**b**) conditions.

Figure 2. Group means for relative delta (1-3.5 Hz), theta (4-7.5 Hz), alpha (8-13 Hz), and beta (13.5-30 Hz) power in the prefrontal cortex (PFC) during the eyes-open (**a**) and eyes-closed (**b**) conditions and in the occipital cortex during the eyes-open (**c**) and eyes-closed (**d**) conditions. Pre = Preadolescents; Mid = Mid-adolescents; Late = Late adolesents. Error bars represent standard error.

Figure 3. Group means for absolute alpha power (8-13 Hz) in the prefrontal cortex (PFC) (**a**) and occipital cortex (**b**) during the eyes-open and eyes-closed conditions. Error bars represent standard error. Significance is indicated for the follow up paired t-tests for the *Location* by *Condition* by *Age Group* interaction (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$). PFC alpha power did not differ between the eyes-open and eyes-closed conditions for preadolescents or mid-adolescents. However, late adolescents had more PFC alpha power during eyes-open than eyes-closed. All age groups had significantly more occipital alpha power during eyes-closed than eyes-open.

Figure 4. Partial regression plots of the residuals for the relationships between pubertal stage and absolute alpha power (8-13 Hz) in the prefrontal cortex (PFC) and occipital cortex during the eyes-open and eyes-closed conditions while controlling for chronological age in males aged 9-17 years. Pubertal stage significantly predicted prefrontal absolute alpha power during the eyes-closed (p = 0.009) (**b**) but not the eyes-open (p = 0.080) (**a**) condition. In contrast, pubertal stage predicted occipital alpha power during both eyes-open (p = 0.004) (**c**) and eyes-closed (p = 0.021) (**d**) conditions.

Highlights

- Prefrontal and occipital spontaneous alpha examined in adolescents aged 9-23 years
- Prefrontal alpha greater when eyes open than eyes closed for 18-23 year olds
- Occipital alpha greater when eyes closed than eyes open for all adolescents
- More advanced pubertal stage predicted reduced alpha in 9-17 year old males

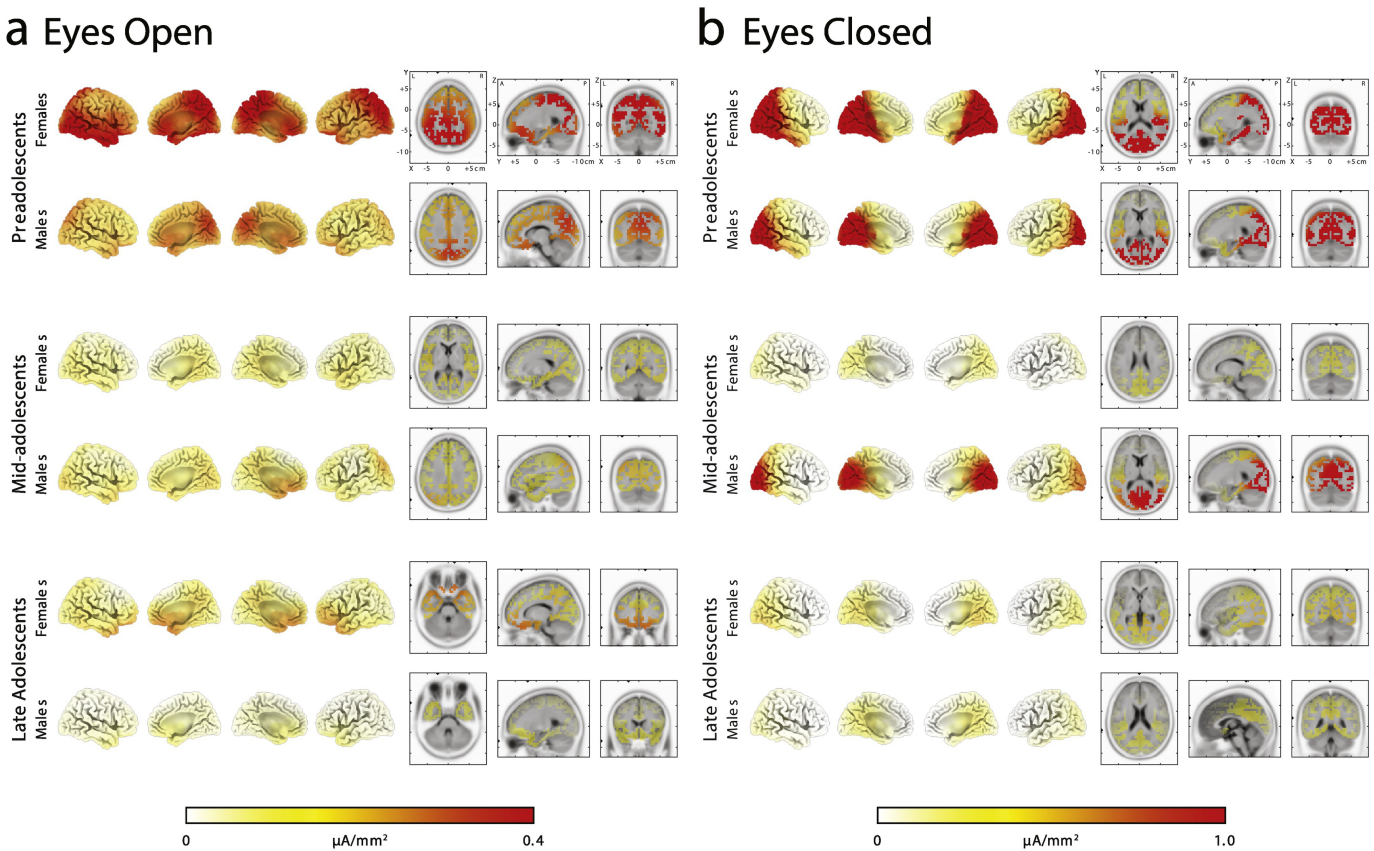
a Eyes Open
b Eyes Closed
Preadolescents
Females
Males
Mid-adolescents
Females
Males
Late Adolescents
Females
Males
0
µA/mm²
0.4
0
µA/mm²
1.0

Figure 1

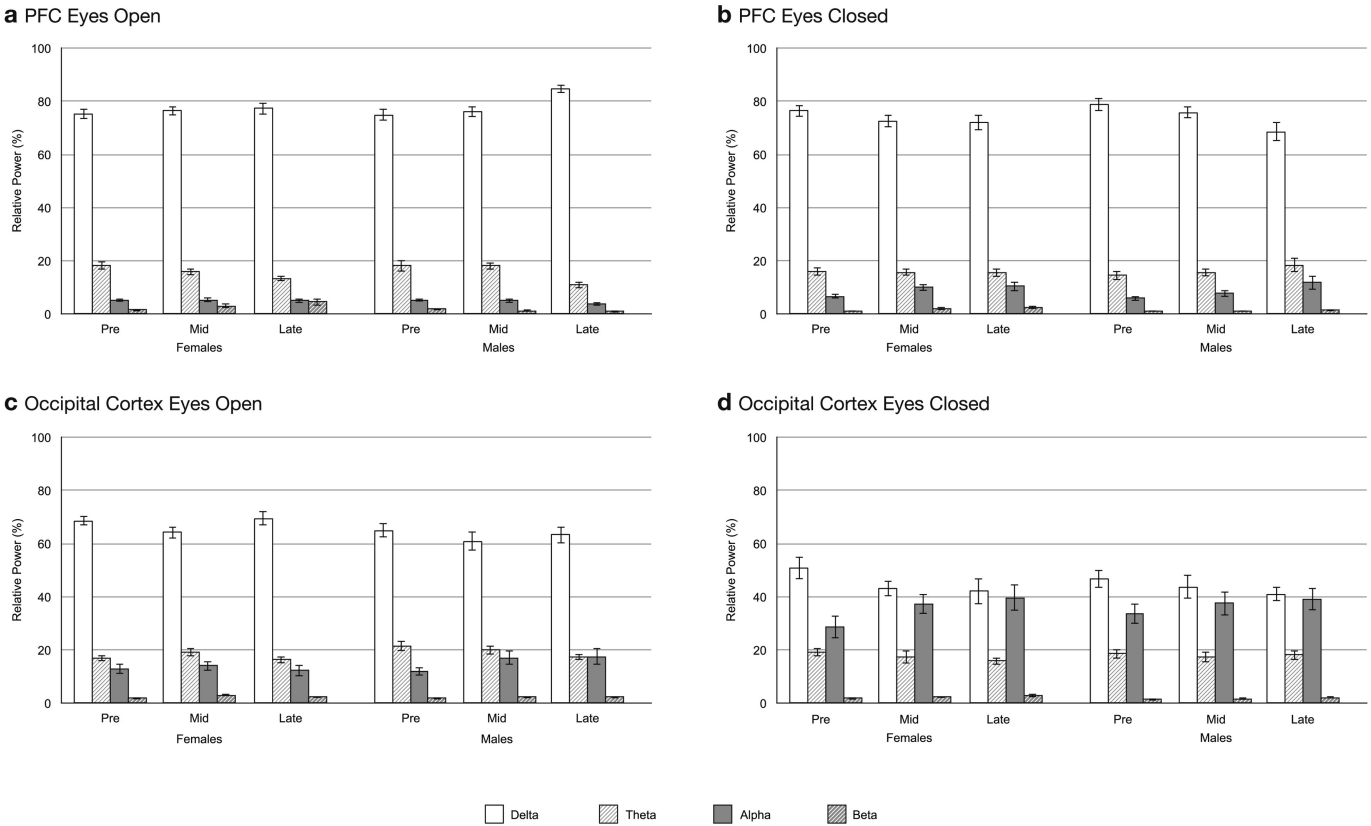
a PFC Eyes Open
b PFC Eyes Closed
c Occipital Cortex Eyes Open
d Occipital Cortex Eyes Closed
Relative Power (%)
0
20
40
60
80
100
Pre
Mid
Late
Females
Males
Delta
Theta
Alpha
Beta

Figure 2

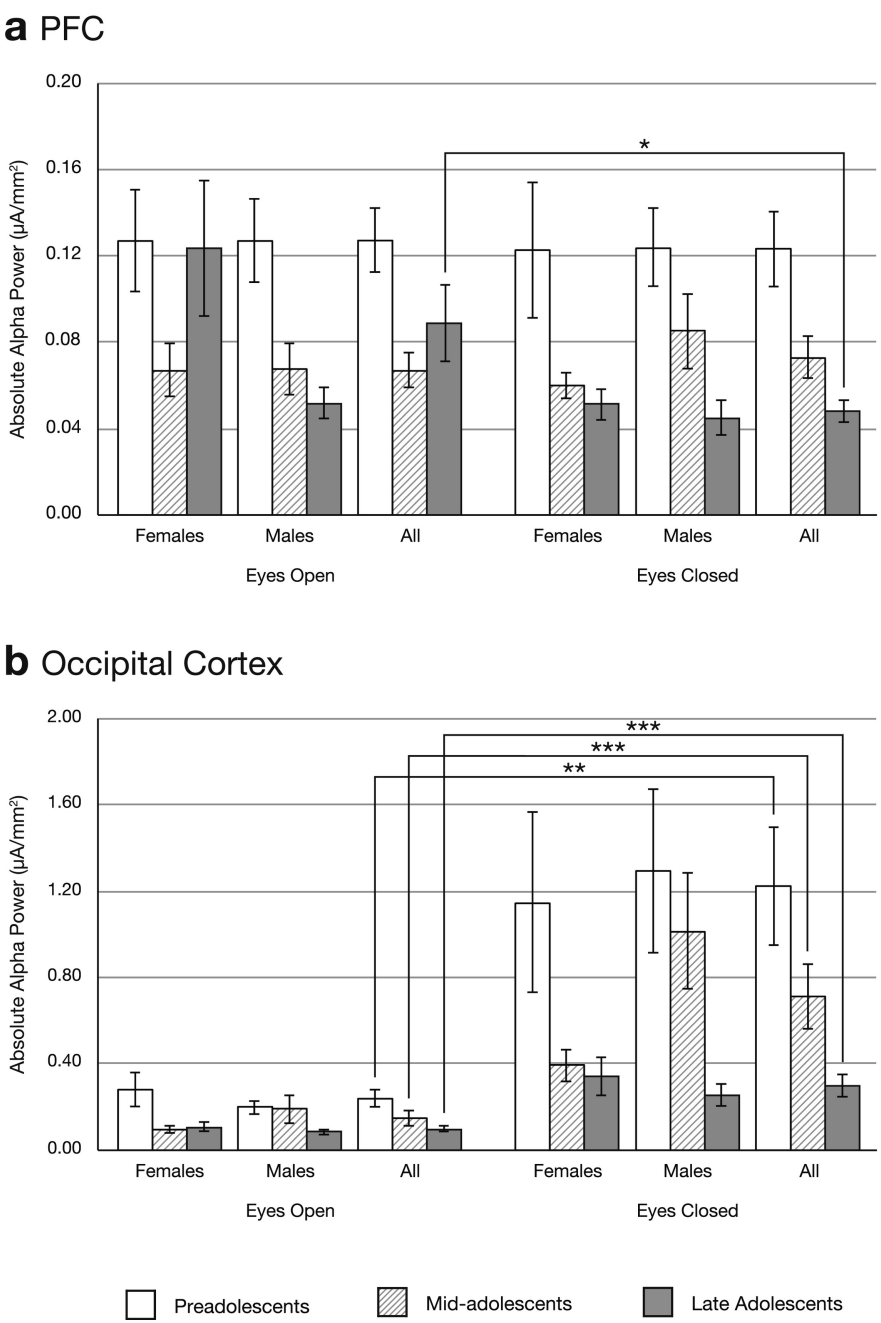
a PFC
Absolute Alpha Power (μA/mm²)
0.20
0.16
0.12
0.08
0.04
0.00
*
Females
Males
All
Females
Males
All
Eyes Open
Eyes Closed
b Occipital Cortex
Absolute Alpha Power (μA/mm²)
2.00
1.60
1.20
0.80
0.40
0.00
***
***
**
Females
Males
All
Females
Males
All
Eyes Open
Eyes Closed
Preadolescents
Mid-adolescents
Late Adolescents

Figure 3

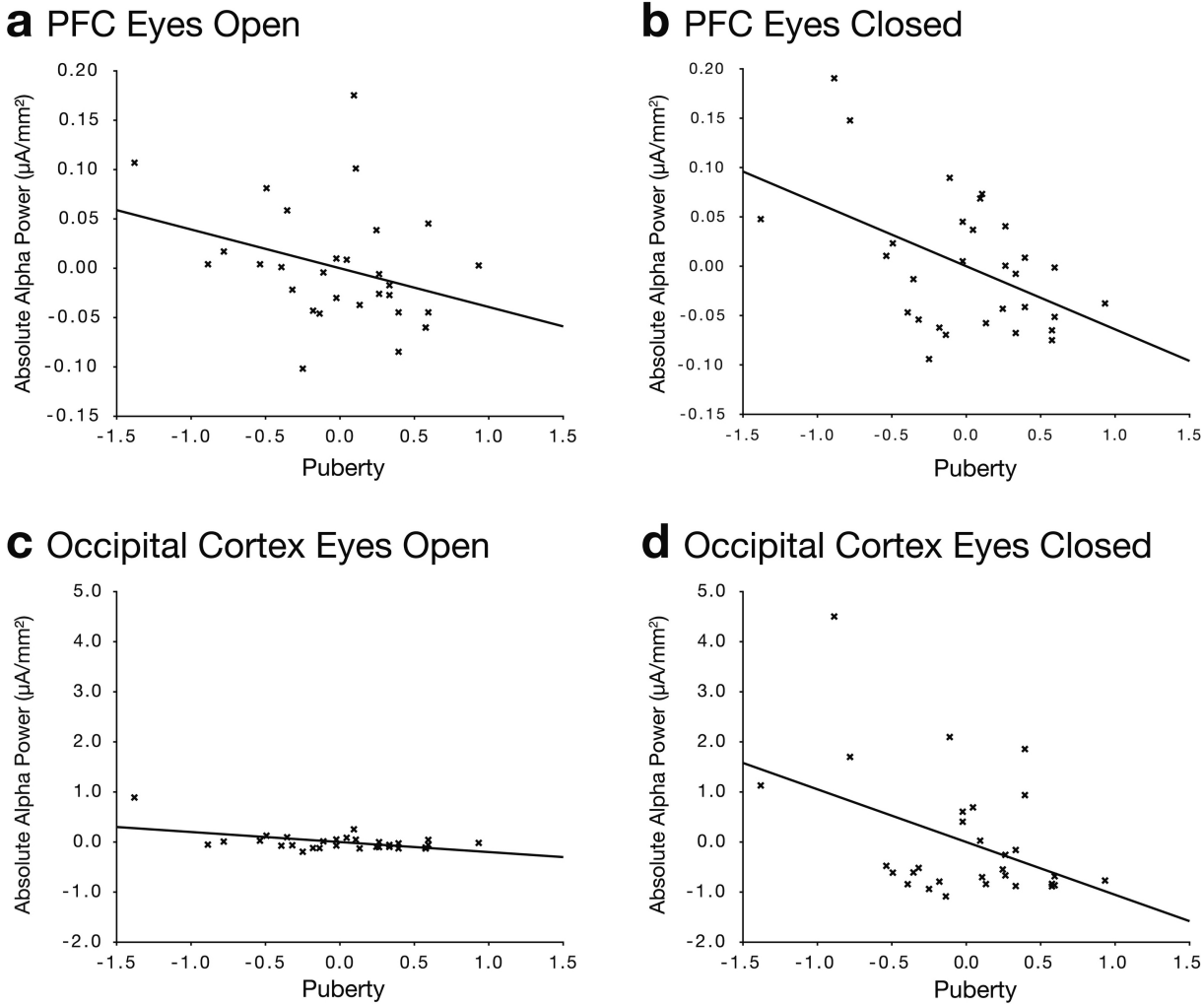
a PFC Eyes Open
b PFC Eyes Closed
c Occipital Cortex Eyes Open
d Occipital Cortex Eyes Closed
Absolute Alpha Power (μA/mm²)
Puberty
0.20
0.15
0.10
0.05
0.00
-0.05
-0.10
-0.15
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
-2.0
-1.5
-1.0
-0.5
0.0
0.5
1.0
1.5

Figure 4